REMARKS/ARGUMENTS

Claims 1-4, 6-12, 14-17 and 37 are under examination in the application. The Office Action mailed on November 3, 2006, includes the following objections and rejections:

1. Claims 1-4, 6-12, 14-17 and 37 are rejected under 35 U.S.C. § 112 second paragraph;
2. Claim 37 is rejected under 35 U.S.C. § 112 first paragraph;
3. Claims 1-4, 6, 8, 9, 15-17 and 37 are rejected under 35 U.S.C. § 102 as being as anticipated.
4. Claims 1-4, 6-12, 14-17 and 37 are rejected under 35 U.S.C. § 103 as being unpatentable.

Applicants assert that a Final rejection is improper at this time as the Action raises new grounds for rejection (a rejected under 35 U.S.C. § 103 as being unpatentable over Parrish, et al. in view of Elbashir) that were not necessitated by an amendment of the claims by the applicants nor based on information submitted in an information disclosure statement. A final rejection is premature when the Action introduces a **new ground** of rejection that is neither necessitated by Applicant's amendment of the claims nor based on information submitted in an information disclosure statement. As such, Applicants respectfully request reconsideration of the finality of the rejection and, therefore, withdrawal of the finality of the action.

Claims 1-4, 6-12, 14-17 and 37 are rejected under 35 U.S.C. § 112, Second Paragraph

The Action rejects claims 1-4, 6-12, 14-17 and 37 under 35 U.S.C. § 112 Second Paragraph as being indefinite. Claims 1 and 37 as amended fully comply with 35 U.S.C. § 112. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112.

The Applicants disagree with the interpretation of claims 1-4, 6-12, 14-17 and 37 in the Action. Claims 1 and 37 of the present application provides an isolated thioaptamer that mediates gene silencing. The isolated thioaptamer includes a partially thiomodified phosphodiester backbone having one or more of the following rAMP(αS), rUMP(αS), rGMP(αS), rCMP(αS), rAMP(αS2), rUMP(αS2), rGMP(αS2) or rCMP(αS2). The phosphodiester backbone has been modified by the addition of one or more of the following rATP(αS), rUTP(αS), rGTP(αS), rCTP(αS), rATP(αS2), rUTP(αS2), rGTP(αS2) or rCTP(αS2) to form a partially thiomodified phosphodiester backbone. Once the modified nucleotide has been added to the phosphodiester backbone it is in the form of a rAMP(αS), rUMP(αS), rGMP(αS), rCMP(αS), rAMP(αS2), rUMP(αS2), rGMP(αS2) or rCMP(αS2). The claims have been

amended to more specifically point out and distinctly claim the subject matter the inventor regards as the invention.

This amendment finds support throughout the application, specifically, the application (paragraphs [0030-0031]) defines the term thioaptamer as oligonucleotides (ODNs) in which one or more of the four constituent nucleotide bases of an oligonucleotide are analogues of nucleotides that normally form the DNA or RNA backbones. The analogues include thiophosphates having sulphur in place of one or more of the non bridging oxygens bound to the phosphorus. For example, monothiophosphates (αS) have only one sulfur and are thus chiral around the phosphorus center; while dithiophosphates (αS2) are substituted at both oxygens and are thus achiral. The modified nucleotide thioaptamer include one or more monophosphorothioate (e.g., dATP(αS), dTTP(αS), dCTP(αS), dGTP(αS), rUTP (αS), rATP(αS), rCTP(αS) or rGTP(αS)) or phosphordithioate (e.g., dATP(αS2), dTTP(αS2), dCTP(αS2), dGTP(αS2), rATP(αS2), rCTP(αS2), rGTP(αS2) or rUTP(αS2)) linkages incorporation by polymerases.

Applicants assert that claims 1-4, 6-12, 14-17 and 37 as amended fully complies with the written description requirement of 35 U.S.C. § 112 first paragraph. Applicant respectfully requests the withdrawal of the rejection under 35 U.S.C. § 112.

Claim 37 is rejected under 35 U.S.C. § 112, First Paragraph

The Action also rejects claim 37 under 35 U.S.C. § 112 as failing to comply with the enablement requirement. Applicants disagree with the interpretation of Opalinska, et al. and asserts that the present application fully complies with the enablement requirement under 35 U.S.C. § 112.

The present application fully enables a pharmaceutical thioaptamer composition having about 21 to about 25 nucleotides that mediates gene silencing and an appropriate carrier. The present application discusses the how to make, characterize and used the pharmaceutical thioaptamer composition (as discussed in prior office action and throughout the specification). Information not present in the application may be supplied by the skilled artisan in the field, e.g., pharmaceutical composition dosage and concentration.

In addition, the skilled artisan is aware that oligonucleotides and thioaptamers are capable of entering the cytoplasm and diffusing into the nucleus to exhibit nuclear localization. The reference cited by the Action (Opalinska, et al.) supports the position that the skilled artisan knows that oligonucleotides and thioaptamers are capable of entering the cytoplasm and diffusing into the nucleus thereby exhibiting nuclear localization. As Opalinska, et al. on page 511, states "…oligonucleotides can escape from the vesicles intact, enter the cytoplasm and then diffuse into the nucleus…" Opalinska, et al. also states that these techniques have been successfully been used both *in-vivo* and *in-vitro* (see Opalinska, et al. second paragraph page 504). Opalinska, et al., even states that "…these small molecules have the ability to diffuse into the nucleus where they can contact dsDNA…" (see Opalinska, et al. page 504). Opalinska, et al. further discusses numerous oligonucleotide treatments which are in clinical trials (see Opalinska, et al. Table 2 on page 511) and that both European and United States authorities have approved a nucleic-acid drug for use to treat a viral infection of the eye (Opalinska, et al. on page 507). Given the numerous oligonucleotide treatments in clinical trials, the government approval of a nucleic-acid drug treatment, and the teachings of Opalinska, et al., the skilled artisan in the area of nucleic-acid drugs and pharmaceutical compositions knows that oligonucleotides and oligonucleotide pharmaceutical compositions may be used as treatments.

The skilled artisan is capable of preparing pharmaceutical compositions for administering to an organism or an individual cell or group of cells. The skilled artisan knows that oligonucleotides and thioaptamers exhibit nuclear localization. The skilled artisan also knows there are other nucleic-acid drugs and oligonucleotide treatments that have already been used for the treatment of various diseases. Therefore, a person of ordinary skill in the art in possession of the present application can prepare pharmaceutical thioaptamer compositions that mediate gene silencings commensurate in scope with claim 37.

Applicants assert that claim 37 fully complies with the requirements of 35 U.S.C. § 112 and respectfully requests the withdrawal of the rejection.

Claims 1-4, 6, 8, 9, 15-17 and 37 are rejected under 35 U.S.C. § 102

The Action also rejects claims 1-4, 6, 8, 9, 15-17 and 37 under 35 U.S.C. § 102(b) as being anticipated by Parrish, et al. (Molecular Cell 2000) ("Parrish"). Applicants respectfully submit that the cited

reference fails to meet the standard of 35 U.S.C. § 102(b) namely, teaching all elements of the claimed invention either explicitly or impliedly and every limitation of the present invention. Even if Parrish did possess every limitation of the present invention Parrish is not prior art and as such still cannot anticipation the present invention.

Parrish is not considered prior art with regards to the present application as the analogues of RNA having sulphur in place of oxygen as one of the non-bridging ligands bound to the phosphorus of the present application predates Parrish. The present application is a continuation in part of United States Patent Number 6,867,289 entitled "Thio-modified aptamer synthetic methods and compositions" issued to Gorenstein, et al. and filed on October 25, 1999 and discloses "analogues of RNA having sulphur in place of oxygen as one of the non-bridging ligands bound to the phosphorus" in column 9, line 48-56 "thiophosphosphate" or "phosphorothioate" are used interchangeably to refer analogues of DNA or RNA having sulphur in place of oxygen as one of the non-bridging ligands bound to the phosphorus. Monothiophosphates [αS] have one sulfur and are thus chiral around the phosphorus center. Dithiophosphates are substituted at both oxygens and are thus achiral. As such, present application incorporates by reference that material from the parent application (now United States Patent Number 6,867,289) and predates the Parrish article of 2000.

Even if Parrish was to be considered prior art, which it is not, it would still fail to disclose and enable each and every element (or limitation) to the claims of the present invention. Parrish discloses that the partially thiomodified phosphodiester backbone having no more than a single modification along the backbone. Specifically, on (page 1081 column 2) Parrish states that they "…were able to demonstrate interference activity following the incorporation of a single modified residue" and further limited the single modification to A, G or C residues. Parrish teaches that the "…RNA with two modified bases also has substantial decreases in effectiveness as RNAi triggers…" and the "…modification of more than two residues greatly destabilized the RNAs…" and they were not able to assay for interference activity (page 1081 column 2). Parrish does not enable the use of a partially thiomodified phosphodiester backbone.

Parrish does not meet the standard of 35 U.S.C. § 102(b) namely, teaching all elements of the claimed invention. Parrish does not teach a partially thio-modified thioaptamer that mediates gene silencing. Parrish does not teach between 15 and 25 nucleotides, an isolated thioaptamer between 15 and 25

nucleotides having a partially thiomodified phosphodiester backbone having rAMP(αS), rUMP(αS), rGMP(αS), rCMP(αS), rAMP(αS_2), rUMP(αS_2), rGMP(αS_2) or rCMP(αS_2). In fact, Parrish does not teach rAMP(αS_2), rUMP(αS_2), rGMP(αS_2) or rCMP(αS_2) for any sequence or any length.

Furthermore, Parrish does not teach a thioaptamer having a perfect or imperfect complementarity match to a target gene, in fact, Parrish teaches that sequence and motifs are unimportant as they "…were able to rule out a specific requirement for any sequence motif in the trigger or target RNA and were able to rule out any requirement for A, U, or C residues in the fragment sequence" (page 1083 column 1).

Additionally, Parrish indicates that the short RNAs may have no role in RNAi and may simply be a product of RNAse digestion (page 1084 column 2). The data from the dsRNAi experiments of Parrish (page 1078 column 2) indicates that the smaller dsRNAi required 250 times the concentration of the larger dsRNAi. Furthermore, the sequences listed in Parrish contain 3 of the 4 nucleotides, e.g., see Figure 1B. Simply, Parrish does not teach an isolated thioaptamer that mediates gene silencing having a partially thiomodified phosphodiester backbone having one or more of the following precursors incorporated therein, e.g., rATP(αS), rUTP(αS), rGTP(αS), rCTP(αS), rATP(αS_2), rUTP(αS_2), rGTP(αS_2) or rCTP(αS_2).

Applicants respectfully submit that claims 1-4, 6, 8, 9, 15-17 and 37 as amended are not anticipated by Parrish. Parrish is non-enabling and does not disclose and enable each and every limitation to the present invention; and as such, cannot anticipation the present invention. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

Claims 1-4, 6, 8, 9, 15-17 and 37 are rejected under 35 U.S.C. § 103(a)

Applicants assert that a Final rejection is improper at this time as the Action raises new grounds for rejection (a rejected under 35 U.S.C. § 103 as being unpatentable over Parrish, et al. in view of Elbashir) that were not necessitated by Applicants' amendment of the claims nor based on information submitted in an information disclosure statement. Under MPEP § 706.07(a) a Final rejection is improper when the Action raises <u>new grounds</u> for rejection that were not necessitated by an amendment of the claims by the applicants nor based on information submitted in an information disclosure statement.

As a premature final rejection is purely a question of practice that is wholly distinct from the tenability of the rejection, applicants respectfully address the grounds for rejection. Applicants assert that the combination of the cited references fail to establish a prima facie case of obviousness.

Parrish is not considered prior art with regards to the present application as the analogues of RNA having sulphur in place of oxygen as one of the non-bridging ligands bound to the phosphorus of the present application predates Parrish.

The Action rejected claims 1-4, 6, 8, 9, 15-17 and 37 under 35 U.S.C. § 103(a) as being unpatentable over Parrish, et al., (hereinafter referred to as "Parrish") in view of Elbashir, et al. (hereinafter referred to as "Elbashir").

In order to establish a prima facie case of obviousness, three criteria must be met: (1) there must be some suggestion or motivation in the prior art to modify the reference or to combine reference teachings as proposed, (2) there must be a reasonable expectation of success, and (3) the prior art or combined references must teach or suggest all the claim limitations. MPEP § 2143; *In re Vacek*, 947 F.2d 488 (Fed. Cir. 1991). "The prior art must suggest the desirability of the claimed invention." MPEP § 2143.01. Both the invention and the prior art references must be considered as a whole. MPEP § 2141.02. Applicants respectfully submit that claims 1-4, 6, 8, 9, 15-17 and 37, as amended, are not obvious over the cited art and are, therefore, allowable under 35 U.S.C. § 103(a) for the reasons stated below.

There is no teaching or suggestion in the prior art to modify the reference as proposed.

Obviousness can only be found where there is some teaching, suggestion, or motivation to modify a reference in the manner proposed, found either in the prior art itself or in the knowledge generally available in the art. See MPEP § 2143.01; *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992). Further, the mere fact that references can be combined or modified does not necessarily make the combination obvious unless the prior art suggests the combination. See MPEP § 2143.01; *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990). Finally, simply stating that a claimed modification of the prior art would have been "obvious to a person of ordinary skill in the art at the time the invention was made" because all aspects of the claimed invention were allegedly known individually in the art is not enough to establish a prima facie case of obviousness without some

objective reason to combine the teachings. MPEP § 2143.01; *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993).

Parrish provides no teaching, suggestion, or motivation to modify a reference in the manner proposed. Parrish, as discussed above and incorporated herein, indicates that the short RNAs may have no role in RNAi and may simply be a product of RNAse digestion (page 1084 column 2). The data from the dsRNAi experiments of Parrish (page 1078 column 2) indicates that the smaller dsRNAi required 250 times the concentration of the larger dsRNAi. Furthermore, the sequences listed in Parrish only contain 3 of the 4 nucleotides, e.g., see Figure 1B and Parrish states that the sequence and motifs are unimportant as they "…were able to rule out a specific requirement for any sequence motif in the trigger or target RNA and were able to rule out any requirement for A, U, or C residues in the fragment sequence" (page 1083 column 1).

Elbashir teaches that the duplexes of RNAs are sequence specific mediators of RNA interferences and post-transcriptional gene silencing (see Elbashir abstract page 6877). These teachings of Elbashir are at odds with the statements of Parrish and there are no teachings, suggestions, or motivations to modify the references in the manner proposed, found either in Elbashir, Parrish, any combination thereof or in the knowledge generally available in the art. Applicants respectfully submit that a person skilled in the art would not combine the teachings of Elbashir and Parrish because they disclose separate and distinct teachings that are incompatible with one another.

There is no expectation of success.

In order to establish a prima facie case of obviousness based on a combination of references, there must be a reasonable expectation of success. Parrish, indicates that the short RNAs may have no role in RNAi, the short RNAs may simply be a product of RNAse digestion, the short RNAs required 250 times the concentration of the larger dsRNAi, and the sequence and motifs are unimportant. In contrast, Elbashir teaches that the duplexes of RNAs are sequence specific mediators of RNA interferences and post-transcriptional gene silencing. For the reasons stated above, Applicants respectfully submit that a person of ordinary skill in the art would have no reasonable expectation of success to modify or combine Elbashir and Parrish and even if the did they would not produce a partially thiomodified phosphodiester backbone having one or more of the following precursors

incorporated therein, e.g., rATP(αS), rUTP(αS), rGTP(αS), rCTP(αS), rATP(αS_2), rUTP(αS_2), rGTP(αS_2) or rCTP(αS_2).

The cited art does not teach or suggest all the claim elements.

Unless the reference(s) teach or suggest all the claim limitations, obviousness cannot be found. MPEP § 2143.03. As mentioned above and incorporated herein Parrish and Elbashir taken individually and/or in any combination do not teach or suggest all the claim limitation of the present invention, specifically, a partially thio-modified thioaptamer that mediates gene silencing with between 15 and 25 nucleotieds having a partially thiomodified phosphodiester backbone having rAMP(αS), rUMP(αS), rGMP(αS), rCMP(αS), rAMP(αS_2), rUMP(αS_2), rGMP(αS_2) or rCMP(αS_2), rAMP(αS_2), rUMP(αS_2), rGMP(αS_2) or rCMP(αS_2) for any sequence or any length with a perfect or imperfect complementarity match to a target gene.

For the reasons stated above, Applicants respectfully submit Parrish and Elbashir taken individually and/or in any combination fail to meet the standard of 35 U.S.C. § 103 namely, they do not disclose teach or suggest all the claim elements, they do not suggestion or motivation the modification of the reference or to combine reference teachings as proposed, and there is no reasonable expectation of success. Furthermore, Parrish is not considered prior art with regards to the present application. Applicants respectfully submit that claims 1-4, 6, 8, 9, 15-17 and 37, as amended, are not obvious over the cited art and are, therefore, allowable under 35 U.S.C. § 103(a) for the reasons stated below.

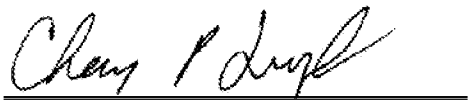
Conclusion

In light of the remarks and arguments presented above, Applicants respectfully submit that the claims in the Application are in condition for allowance. Favorable consideration and allowance of the pending claims is therefore respectfully requested.

If the Examiner has any questions or comments, or if further clarification is required, it is requested that the Examiner contact the undersigned at the telephone number listed below.

Dated: April 3, 2007

Respectfully submitted,



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